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(19)(CA) **CANADIAN PATENT** (12)

(54) Implantable, Biodegradable System for Releasing Active Substance

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Biodegradable implant

The present invention relates to a biodegradable implant, i.e. an implantable system for releasing an active substance.

Numerous implantable or injectable systems for releasing active substance are known from the prior art. Systems of this kind are preferably used when an active substance has to be administered over a fairly long period of time and oral administration is impossible or unreliable or impractical. In addition to use in humans, parenteral preparations for use in animal husbandry or for the treatment of animal diseases are of special interest. The conventional method of administering drugs by adding them to the feed has the serious disadvantage that the quantity of drug taken is not sufficiently accurate.

Implantable systems for releasing active substance should satisfy the following criteria:

The active substance should be released at a constant rate over a long period of time and the implant should be broken down within a reasonable interval after the active substance has been released so that there is no need to operate to remove the implant. It is also advantageous if the rate of release of active substance from the carrier can be made variable so that it can be matched both to the active substance and also to the particular treatment.

An objective of this invention is to provide a biodegradable implant which can release an active substance over a fairly long period of time at a substantially constant rate and which can be broken down within a reasonable time.

We have found that this objective may be achieved by means of an implant comprising a poly-D,L-lactide-based, additive-containing carrier material.

Thus, in one aspect the present invention provides a biodegradable implant comprising a poly-D,L-lactide based, physiologically active substance containing carrier material and, optionally, at least one pharmaceutical excipient, said carrier material further containing at least one additive material selected from pore-forming agents, low molecular weight polymers, and up to about 10% by weight relative to the carrier material weight of physiologically acceptable solvents or plasticizers.

In the active substance releasing implants of the invention, the additive materials in the carrier material are conveniently selected from: physiologically acceptable solvents or plasticizers, preferably acetic acid esters, in an amount of up to 10% by weight; suspended water-soluble pore-forming agents, such as for example lactose, in an amount of up to 50% by weight; low molecular weight polymers, preferably biodegradable polymers, especially preferably polymers and copolymers of lactic acid and glycolic acid, in an amount of up to 60% by weight; the weight percentages being relative to the carrier material weight.

Poly-D,L-lactides having a wide range of molecular weights are known. For the carrier material of

the implant according to the invention, poly-D,L-lactides with mid-range number average molecular weights are preferred, for example polymers having an inherent viscosity of between 0.15 and 4.5 (measured in chloroform at 25°C, at a test concentration C of 100 mg/ml).

In a preferred embodiment of the invention, the carrier material consists of poly-D,L-lactide.

In another embodiment of the invention, the carrier material comprises a copolymer of D,L-lactide and glycolide; in this embodiment the portion of glycolide in the copolymer should not exceed 50% by weight.

Surprisingly, it has been found that the rate of decomposition of the implant of the invention can be controlled by incorporating in the carrier material a defined content of a physiologically acceptable solvent or plasticiser, such as an acetic acid ester, or a mixture of solvents which will quantitatively remain in the polymer even after lengthy storage. This is of crucial importance, since on the one hand the implant must be broken down rapidly enough but on the other hand excessively rapid decomposition of the implant will lead to uncontrolled release of the active substance. The solvent or plasticiser, preferably an acetic acid ester, is incorporated in the carrier material in amounts of up to 10% by weight relative to the weight of the carrier material whereby increasing amounts of the solvent or plasticiser will accelerate the breakdown of the carrier material. A composition which gives a release of active substance corresponding to a half-life of between 3 and 60 days, followed by breakdown of the implant within about 120 days thereafter is favourable. In individual cases,

however, shorter rates of release and breakdown may be advantageous.

Surprisingly, it has also been found that, although the incorporation of the poly-D,L-lactide solvent or plasticiser (e.g. an acetic acid ester) influences the rate of decomposition of the implant it has no significant effect on the release of the active substance.

Acetic acid esters which can be used for the purposes of the invention include the alkyl esters of acetic acid, such as the C_{1-5}alkyl esters, e.g. the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert.-butyl, n-pentyl, sec.-pentyl, isopentyl and tert.-pentyl esters. Ethyl acetate is particularly preferred.

The rate of decomposition of the implant may also be controlled by the addition of low molecular weight polymers. Thus in another embodiment, the implant according to the invention may contain up to 60% (by weight relative to the weight of the carrier material) of low molecular weight polymers such as, for example, poly(L-lactic acid), poly(D-lactic acid), poly(D,L-lactic acid), poly(glycolic acid), poly(L-lactic acid-co-glycolic acid), poly(D-lactic acid-co-glycolic acid) and poly(D,L-lactic acid-co-glycolic acid). Poly(L-lactic acid) and poly(D,L-lactic acid) are preferred. For these low molecular weight polymers the number average molecular weights (determined by titration of the terminal groups) conveniently range from 500 to 5000, preferably from 1500 to 2500.

The incorporation of these polymers into the carrier material, either on their own or in conjunction

with a solvent or plasticizer such as an acetic acid ester, makes it possible to control the rate of decomposition of the implant.

Besides influencing the decomposition rate of the implant by incorporating polymers, solvents or plasticizers into the carrier material, it is also possible to influence the active substance release rate, for example:

a) by incorporating into the carrier material a pore-forming agent, such as for example lactose,
b) by selecting the physical state of the active substance (e.g. in solution, in suspension or in particulate form having particular particle sizes),
c) by selecting the physical form of the carrier material (e.g. monolithic, polydispersed, or laminated forms).

Therefore, in addition to compounds which influence the rate of decomposition of the carrier material, the implant according to the invention may also contain additive substances in the form of pore-forming agents which make it possible to control the release of active substance.

Pore-forming agents which may be used according to the invention include, for example, water soluble pharmaceutically acceptable monosaccharides and disaccharides. Lactose is preferred, but glucose, fructose, xylose, galactose, sucrose, maltose, saccharose and related compounds such a mannitol, xylitol and sorbitol may also be used. Other suitable excipients which may be used include salts such as the lactates, glyconates or succinates of sodium, potassium or magnesium.

Rapid and immediate release of the active substance from the carrier material immediately after implantation is achieved when the rate of release of the pore-forming agent is very much greater than that of the active substance. This is the case, for example, when the pore-forming agent, e.g. lactose, has good solubility and a small particle size. A retarded accelerated release of the active substance is achieved when the solubility of the pore-forming agent is very much less than that of the active substance; this occurs, for example, when the pore-forming agent has poor water solubility. The delayed accelerated release of the active substance ensures that the linear release curve of the active substance is reliably ensured even over long periods of administration.

Using the parameters described, it is possible to produce implants which have individually selected release and breakdown rates.

The implant according to the invention in monolithic form (i.e. in the form of a continuous mass) may be implanted or injected. Conveniently the monolithic implants are in the form of rods or tubular members. The rods are conveniently of such dimensions that they can be implanted by means of an injection needle or a trocar. A rod may be, for example, about 3 cm long and about 2.8 mm in diameter.

Certain exemplary embodiments of the invention will be described hereinafter with reference to the accompanying drawings, in which:-

Figure 1 is a schematic partial cross-section through an implant according to the invention in encased hollow tubular member form (type E);

Figure 2 to 7 and 11 are graphs showing the degradation with time of implants according to the invention;

and Figures 8 to 10 and 12 are graphs showing the active substance release with time of implants according to the invention.

The following embodiments of the implant of the invention, described hereinafter, are preferred:

A) solid rods
B) rolled up films
C) encased rods
D) tubular members
E) encased tubular members

All the embodiments of the implant according to the invention may be of laminated construction and may be produced, for example, by the following methods, which themselves represent further aspects of the invention.

Thus in another aspect, the present invention provides a process for the preparation of implants according to the invention, which process comprises: forming a solution of said carrier material containing said at least one additive material, said physiologically active substance and, optionally, at least one said pharmaceutical excipient; pouring said solution to form a film; at least partially removing the solvent from said film to form a dried film; and forming one or more said dried films into a tubular or rod-like member of desired dimensions.

The active substance may be distributed within, e.g. dissolved or suspended with, the dissolved polymeric carrier material, e.g. with ethyl acetate

as solvent, and the additive material or any further additive material may be combined therewith. If desired, other pharmaceutical adjuvants may be added to the dissolved polymeric carrier material in addition to the active substance and the additive material. The carrier material solution is then poured out onto a surface and dried, i.e. the solvent is at least partially removed, to form a film. The drying conditions may particularly preferably be chosen so that a desired residual amount of solvent remains in the polymeric carrier material, generally an amount of between 1 and 7% by weight. The dried films preferably have a layer thickness of between 30 and 1000 micrometers, especially preferably about 100 micrometers. Apparatus and methods for producing these films are known to those skilled in the art and require no further comment. It goes without saying that the drying process must be carried out with a certain degree of care (e.g. slowly and with minor variations in temperature and vacuum humidity) to ensure that the films stay flat.

Multi-layer films may be obtained by re-applying polymer solution (with or without active substance).

After the film is dry it may be cut up into rods of the desired length to form implants of type A.

Implants of type B may be produced by rolling up into rod like shapes one or more single- or multi-layer films. The film or at least one of the films used will contain the active substance. However, the thickness of the films used to produce the implants of type B may be substantially less than those used to produce the implants of type A, films

of between 30 and 500 micrometers, preferably between 70 and 90 micrometers, generally being used. After drying, the films are cut and rolled up into rods of the required diameter, e.g. up to about 3 mm, which may then be cut to the desired length. The rods may be rolled up so as to leave a central cavity. In constructing a laminated implant of type B, it is also possible to lay several films one over the other or, preferably, to pour them one over the other and then to roll them up to form a rod. By combining several layers of film, active substances can easily be combined and layers with different concentrations of active substance can be used. The individual layers may thus have different release rates.

As well as an alternating layer sequence it is also possible to produce a rolled core and then to apply additional layers of film on the outside.

By using layers of film with different release characteristics, it is possible to produce an implant which will release different active substances in a predetermined time sequence. It is not absolutely necessary for all the film layers to contain active substances.

When producing the implant of type B according to the invention, the films should preferably have a relatively high content of residual solvent (e.g. about 10%) when they are rolled up. This prevents the films from becoming brittle. Once rolled up, the rod may then be subjected once more to a drying process in order to achieve the desired residual solvent content.

Alternatively, implants of types C, D and E may advantageously be produced by extrusion or injection moulding of granules of active substance and carrier material polymer or copolymer, optionally together with additives such as polylactic acid, a plasticiser such as triacetin or a pore-forming agent such as lactose.

Thus in a still further aspect the invention provides a process for the preparation of implants according to the invention, which process comprises extruding a mixture of said carrier material, physiologically active substance, additive material and, optionally, pharmaceutical excipient and forming the extrudate into tubular or rod-like members of desired dimensions.

The tubular or rod-like implant may, if desired, also be provided with an outer casing which may be permeable or impermeable to the active substance. The release of active substance from the encased forms C and E may take place by various methods depending on the construction of the implant used. Implants of type C contain a solid core containing the active substance and are surrounded by a "porous" casing. The active substance suspended in the core diffuses through pores in the casing created by the dissolving out of a pore forming agent, lactose for example. The critical release factors therefore include the degree of charging of the casing and the particle size of the pore-forming agent, e.g. lactose.

By contrast with the encased forms of type C, the implant of type E consists of a hollow tubular member containing the active substance, the outer surface of which is encased in a sheath which is impermeable to the active substance.

with implants of type E, provided that the casing is free from pores and impervious, the active substance in the tubular member can only be released into the central cavity of the tubular body. In this sytem, the channels, i.e. diffusion paths for the active substance, lengthen with time, and this is compensated for by the increasing quantity of active substance in a segment as the distance from the cylinder axis increases.

Referring to the accomanying drawings, figure 1 is a schematic cross section through an embodiment of an implant according the invention of type E. The tubular core has a hollow central cavity 3, contains particles 2 of active substance and is provided with an outer impervious casing 1.

Crucial release factors for implants of type E, in addition to the breakdown of the polymeric carrier material and the degree of charging, include the dimensions of the tubular implant such as its length and internal diameter. It goes without saying that, in the case of implants of type E, the casing which is impervious to the active substance is also biodegradable. Conveniently it comprises a biodegradable polymer, preferably a poly-D,L-lactide. A major advantage of the implants thus formed is that the active substance is released in a substantially linear manner.

Implants of this type may also be produced using films produced as described hereinbefore, the outer film consisting of a layer which is free from and impervious to the active substance.

Experiments have shown that the implants produced by the "solvent method" (types A and B for example)

have different breakdown characteristics from implants produced by extrusion, i.e. the extruded members are broken down more slowly despite having the same polymer composition (see Fig. 2 hereto). The difference may be due to the fact that in extrusion it is not readily possible to achieve a defined, higher residual solvent content because of the relatively high temperatures during extrusion.

Implants according to the invention produced by extrusion or injection moulding may conveniently be produced using a carrier material comprising a poly-D,L-lactide having a inherent viscosity of between 0.15 and 1.0. Polymers of low inherent viscosity (η = 0.15) may be processed even at temperatures below 100°C, which is advantageous for the thermal stress on the drugs added thereto.

Implants produced from a low inherent viscosity poly-D,L-lactide not only release the active substance more rapidly but also show faster decomposition of the implant than is the case with polymers with higher inherent viscosities (greater than 0.3), which means that, if desired, an implant may be produced which breaks down after only about 10 weeks.

Low viscosity poly-D,L-lactides may be prepared from higher viscosity poly-D,L-lactides by partial hydrolysis.

The release of active substance from the implants according to the invention may be delayed by providing an additional coating of low molecular weight poly-D,L-lactide which contains no active substance but which is permeable to the active substance. This prevents the active substance from being released

too quickly in the initial phase directly after implanting.

Suitable active substances for incorporation in the implants of the invention include those which may be distributed in suspensed form in the polymeric carrier material, especially the water-soluble salt forms of bases, such as hydrochlorides or hydrobromides. Clenbuterol hydrochloride is particularly preferred.

Furthermore, in the field of veterinary medicine, the groups of substances and compounds listed below may be used in the implants according to the invention.

glucocorticoids for inducing labour, e.g. dexamethasone, betamethasone, flumethasone, the esters and derivatives thereof, gestagens for synchronising heat, or for suppressing heat and rut;

β_2-adrenergics for the treatment and prevention of respiratory diseases, for preventing abortion and birth, for promoting growth and influencing the metabolism, such as clenbuterol, ethyl 4-(2-tert.-butylamino-1-hydroxyethyl)-2-cyano-6-fluoro-phenylcarbamate hydrochloride, α-[[[3-(1-benzimidazolyl)-1,1-dimethylpropyl]-amino]-methyl-2-fluoro-4-hydroxy-benzylalcohol methanesulphonate monohydrate, 1-(4-amino-3-cyanophenyl)-2-isopropylaminoethanol;

β-blockers for the prevention of Mastitis Metritus Agalactie (MMA), for reducing travel stress, α_2-adrenergics against enteritic diseases and for the treatment of hypoglycaemic conditions, and for sedative purposes (e.g.

clonidine, 2-[2-bromo-6-fluorophenylimino]-imidazolidine;

benzodiazepines and derivatives thereof such as brotizolam for sedative purposes;

antiphlogistics for anti-inflammatory treatment, e.g. meloxicam;

somatotropin and other peptide hormones for increasing yield;

endorphins for stimulating movement in the rumen;

steroid hormones (natural and synthetic) for promoting growth, e.g. oestradiol, progesterone and the esters and synthetic derivatives thereof such as trenbolon;

anti-parasitics for controlling endo- and ectoparasites, such as avermectin; ; and

cardiac and circulatory substances such as etilefrin or pimobendan.

The implants according to the invention may advantageously be used in human medicine for administering hormones, particularly for contraception, or as cytostatics.

It is possible to use active substances which have both a systemic and a local effect.

A preferred field of use of the implants according to the invention is local cancer therapy.

Thus in a yet still further aspect, the present invention provides a method of therapeutic or prophylactic treatment of the human or non-human animal body which method comprises implanting in said body a physiologically active substance containing implant according to the invention.

The Examples which follow serve to illustrate the invention without restricting its scope in any way.

In the Examples the following polymers are used:

Poly-D,L-lactide I $[\eta]$ = 1.0 (100 ml/g) MW* = 123,000
Poly-D,L-lactide II $[\eta]$ = 2.2 (100ml/g) MW = 300,000
Poly-D,L-lactide III MW = 11,500
Poly-D,L-lactic acid (MW = 2000)

η = intrinsic viscosity

MW = molecular weight

* Determined by gas phase chromatography (standard: polystyrene)

The Examples refer to intrinsic viscosity ( ) which is determined from the inherent viscosity when test concentration C tends to zero; in practical terms under the experimental test conditions, the intrinsic and the inherent viscosities are the same.

Unless otherwise stated, all percentages used herein are by weight and all molecular weights are number average molecular weights.

The Examples are discussed with reference to the following Figures:

Figure 2 which is a graph showing the reduction in molecular mass of the polylactide implants.

($[\eta]$ = intrinsic viscosity
test conditions in vitro: isotonic phosphate buffer pH 7.4; 37°C

A: Rolled rod of poly-D,L-lactide I (solvent method)
B: Extruded cylinder of poly-D,L-lactide I
C: poly-D,L-lactide I powder)

Figure 3 which is a graph showing the reduction in molecular mass of the polylactide implants.

(Test conditions in vitro: isotonic phosphate buffer pH 7.4; 37°C

Preparation: rolled rods of polylactide (solvent method)
A: poly-D,L-lactide I; 7% ethyl acetate, Tg = 26°C
D: poly-D,L-lactide II; 7% ethyl acetate, Tg = 30°C
E: poly-D,L-lactide; 7% ethyl acetate, Mp = 172°C (comparison example))

Figure 4 which is a graph showing the reduction in molecular mass of the poly-D,L-lactide implants.

(Preparation: multi-layer film rolls, batch D
A. Administration: in vivo, sheep, s.c.
B. in vitro, test conditions: isotonic phosphate buffer; pH 7.4; 37°C)

Figure 5 which is a graph showing the reduction in molecular mass of the poly-lactide implants.

(Preparation: rolls of film of poly-D,L-lactide ($[\eta]$ = 2.9 (100 ml/g));
Batch D

A. In vitro test conditions: isotonic phosphate buffer; pH 7.4; 37°C

B. Administration: in vivo, sheep, s.c.)

Figure 6 which is a graph showing the reduction in molecular mass of the polylactide implants.

(Test conditions in vitro: isotonic phosphate buffer; pH 7.4; 37°C

Preparation: rolls of film (solution method)

A: poly-D,L-lactide I; 7% ethyl acetate; Tg = 26°C

F: poly-D,L-lactide I: 1% ethyl acetate; Tg = 48°C

G: poly-D,L-lactide I; 4% ethyl acetate; Tg = 35°C

H: poly-D,L-lactide II; 1% ethyl acetate; Tg = 52°C

I: poly-D,L-lactide II + 50% poly-D,L-lactic acid; 1% ethyl acetate; Tg = 30°C)

Figure 7 which is a graph showing the reduction in molecular mass of the poly-D,L-lactide implants.

(In vitro test conditions: isotonic phosphate buffer; pH 7.4%; 37°C

Preparation: rolls of film (solvent method)

A: poly-D,L-lactide I; 7% ethyl acetate; Tg = 26°C

F: poly-D,L-lactide I; 1% ethyl acetate; Tg = 48°C

G: poly-D,L-lactide I; 1% ethyl acetate; Tg = 35°C

H: poly-D,L-lactide II; 1% ethyl acetate; Tg= 52°C

I: poly-D,L-lactide II + 50% polylactic acid 1% ethyl acetate; Tg = 30°C)

Figure 8 which is a graph showing Methotrexate (MTX) release from polylactide implants.

(Preparation: multi-layer rods of poly-D,L-lactide ($[\eta]$ = 2.2 (100 ml/g)),

A. Administration: rat, intracerebral
B. In vitro conditions: isotonic phosphate buffer; pH 7.4; 37°C)

Figure 9 which is a graph showing release of clenbuterol from poly-D,L-lactide implants.

In vitro test conditions: isotonic phosphate buffer; pH 7.4; 37°C

Preparation: 3-layer film rolls ($[\eta]$ = 2.2 (100 ml/g)) with 23.5% by weight of clenbuterol. HCl and 4% ethyl acetate

Lactose (% by weight)

	1st layer	2nd layer	3rd layer
K	0	0	0
L	0	25%	0

Figure 10 which is a graph showing release of clenbuterol from poly-D,L-lactide implants.

(In vitro test conditions isotonic phosphate buffer; pH 7.4; 37°C.

Preparation: 3 layer film rolls containing 10% by weight of lactose and 23.5% by weight of clenbuterol.HCl poly-D,L-lactide II ($[\eta]$ = 2.2 (100 ml/g)
Additives: L: 4% ethyl acetate
M: 1% ethyl acetate
N: 1% ethyl acetate + 25% poly-D,L-lactic acid)

Figure 11 which is a graph showing reduction of mass of poly-D,L-lactide implants.

(Preparation: double walled tubular implant of poly-D,L-lactide III (see Example 6)
In vitro test conditions: isotonic phosphate buffer pH 7.4, 37°C.)

and Figure 12 which is a graph showing release of clenbuterol from poly-D,L-lactide implants.

(Preparation: double-walled tubular implant of poly-D,L-lactide III (see Example 6)
In vitro test conditions: isotonic phosphate buffer pH 7.4; 37°C.)

Example 1

Effects on polymer decomposition of the method of processing, and the tacticity and molecular mass of the carrier material polymer

25 g of poly-D,L-lactide I are dissolved in 75 g of ethyl acetate and spread out with a doctor blade on a smooth surface to form a film. After drying for at least 24 hours this is repeated twice or three times until a multi-layer film 250 micrometers thick has been produced. The film is then dried first at 23°C and then at 40°C *in vacuo* until a predetermined residual solvent content is obtained, cut into 3 x 2.5 cm pieces and shaped into rolls (3 cm long, 2.8 mm diameter).

Implants produced by the solvent method have different characteristics to implants obtained by extrusion, for example, with regard to their decrease in molecular mass in a buffer solution, i.e. they are advantageously broken down more rapidly (see Fig. 2). The tacticity of the polymer plays a greater part in the rate of breakdown than the molar mass or intrinsic viscosity $[\eta]$ (see Fig. 2). The fact that the rate of breakdown *in vitro* corresponds well to the *in vivo* values is shown by Fig. 4.

A significant reduction in mass occurs after about 70 days both *in vivo* and *in vitro*, i.e. after the limiting viscosity has fallen to a value of $[\eta]$ = 0.3 (100 ml/g) (see Fig. 5).

The administration of the implants to sheep, rats and mice did not produce any special reactions over the observation period (up to 140 days), i.e. the implants were well tolerated locally (see Table 1).

Instead of using the solvent method, correspondingly constructed shaped articles may also be produced by extrusion (core with casing) of granules of polymer, active substance and additives.

Example 2

Effects on polymer breakdown of the residual ethyl acetate content and the addition of polylactic acid

Multi-layer rolls of film are produced as described in Example 1, except that in batch I 50% of the poly-D,L-lactide is replaced by poly-D,L-lactic acid (molecular weight 2000).

Fig. 6 shows that the decrease in molecular weight or mass in an aqueous medium is accelerated by a residual ethyl acetate content of 4 or 7% but not by a content of 1%. The addition of 50% of poly-D,L-lactic acid results in a very marked acceleration of polymer decomposition.

The reduction in mass correlates with the reduction in molecular mass a described in Example 1 (see Fig. 7).

Example 3

Effects of substrate structure on release of active substance

25 g of poly-D,L-lactide II ($[\eta]$ = 2.2 (100 ml/g)) are dissolved in 75 g of ehtyl acetate, 5.0 g of methotrexate (MTX) (particle size 30 micrometers $\leq x \leq$ 60 micrometers) are suspended therein and three-layer films are produced analogously to Example

1 with a layer thickness of 0.80 mm, the upper and lower polymer layers remaining free from active substance. After a residual solvent content of 7% has been obtained, the multi-layer film is cut into strips of 1 x 1 x 10 mm (unlike Example 1).

MTX is released from implants of this kind at a constant rate of 63 micrograms per day in the period from 10 to about 60 days, both in vivo and in vitro, without any significant reduction in the polymer molecular mass (see Fig. 8).

Example 4

Effects of lactose addition on the release of active substance

8.8g of poly-D,L-lactide II ($[\eta]$ = 2.2 (100 ml/g)) are dissolved in 45 g of ethyl acetate and 2.7 g of clenbuterol.HCl (20 micrometers $\leq$ x $\leq$ 53 micrometers) are suspended therein and a three-layer film is prepared as in Example 1. In batch L, an additional 25% by weight of lactose (particle size: 1 - 5 micrometers) is suspended in the polymer solution which is used to form the central layer.

Fig. 9 shows that the addition of lactose accelerates the release of clenbuterol in an aqueous medium and thus provides a method of controlling the release.

Example 5

Effects of polylactic acid addition on the release of active substance

The three-layered film roll L of Example 4 is compared with a preparation produced analogously in which

25% of the poly-D,L-lactide II is replaced by poly-D,L-lactic acid (molecular mass 2000).

Whereas the release of clenbuterol in an aqueous medium is greatly accelerated by the addition of polylactic acid, the residual ethyl acetate content in the range from 1 - 4% had no effect on the release characteristics.

Polylactic acid can therefore be used like lactose as an additive which will control the release of the active substance.

Example 6

Effects of the substrate structure on the release of active substance (Implant type E)

Poly-D,L-lactide III containing no active substance and a fusion granulate consisting of 3 parts by weight of poly-D,L-lactide III and 1 part by weight of clenbuterol hydrochloride (20 - 53 micrometers) are processed at 90°C (mass temperature) to form a double-walled tube (this can be done either by using a suitable extruder or by injection moulding). An implant of type E - produced according to Example 6 - having the following dimensions was used for in vitro tests on the breakdown of polymer and release of active substance: length 10 mm, diameter of central cavity 2 mm, overall diameter 5mm; outer casing (free from and impervious to active substance), wall thickness 0.5 mm; inner tube containing active substance, wall thickness 1.0 mm.

Fig. 11 shows the substantially linear breakdown of the polymer mass in vitro with a half life of about 70 days whilst Fig. 12 shows the substantially linear release of clenbuterol.

Table I Pathology and histology of the implants

Species	Administration	Findings: up to about 60 days: slight capsule formation, slight inflammation, usual macrophage formation; individual cell detritus	Findings: from about 100 days: slight scarring, no inflammation and no other findings
Sheep	s.c., behind the ear	reaction normal	yes
Mouse	s.c. neck	reaction normal	yes
	s.c. back	reaction normal	yes
Rat	intracerebral	reaction normal	yes
	intratumoral, back	reaction normal	yes

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A biodegradable implant comprising a poly-D,L-lactide based, physiologically active substance containing carrier material, said carrier material further containing at least one additive material selected from pore-forming agents, low molecular weight polymers, and up to about 10% by weight relative to the carrier material weight of physiologically acceptable solvents or plasticizers.

2. An implant as claimed in claim 1 wherein said carrier material contains at least one said additive material selected from: water-soluble pore-forming agents in an amount of up to 50% by weight; low molecular weight polymers of lactic or glycolic acid in an amount of up to 60% by weight; and physiologically acceptable solvents or plasticizers in an amount of up to 10% by weight; the percentages by weight being relative to the weight of the carrier material.

3. An implant as claimed in claim 1 wherein said carrier material consists of poly-D,L-lactide.

4. An implant as claimed in claim 1, 2 or 3 wherein said carrier material comprises a copolymer of D,L-lactide and glycolide, having a glycolide content not exceeding 50% by weight.

5. An implant as claimed in claim 1, 2 or 3 wherein said carrier material contains up to 10% by weight relative to the carrier material weight of an acetic acid ester.

6. An implant as claimed in claim 1, 2 or 3, wherein said carrier material contains up to 60% by weight of low molecular weight polylactic acid or up to 50% by weight of lactose, the percentages by weight being relative to the carrier material weight.

7. An implant as claimed in claim 1, 2 or 3 in the form of a tubular or rod-like member.

8. An implant as claimed in claim 7 wherein said member has a layered structure.

9. An implant as claimed in claim 7 which comprises at least one rolled film.

10. An implant as claimed in claim 9 comprising at least one rolled multi-layered film.

11. An implant as claimed in claim 7 which comprises a multi-layer rolled film having layers of different compositions.

12. An implant as claimed in claim 1, 2 or 3 in the form of a hollow active substance containing tubular member provided with an outer casing which is impermeable to said active substance.

13. An implant as claimed in claim 1, 2 or 3, containing as active substance a hormone or cytostatic agent.

14. An implant as claimed in claim 1, 2 or 3 containing clenbuterol hydrochloride as physiologically active substance.

15. A process for the preparation of an implant as claimed

in claim 1 which process comprises : forming a solution of said carrier material containing said at least one additive material, said physiologically active substance pouring said solution to form a film; at least partially removing the solvent from said film to form a dried film; and forming one or more said dried films into a tubular or rod-like member of desired dimensions.

16. A process as claimed in claim 15 wherein removal of said solvent to yield said dried film is so effected as to leave a residual solvent content of about 10% by weight relative to the carrier material weight.

17. A process as claimed in claim 16 wherein after said removal of solvent at least one further carrier material layer is deposited on said film and solvent removal is effected to form a multi-layer dried film.

18. A process as claimed in claim 15, 16 or 17 wherein solvent removal is so effected on said film or on said tubular or rod-like member formed therefrom as to leave a residual solvent content of from 1 to 7% by weight relative to the carrier material weight.

19. A process as claimed in claim 15, 16 or 17 wherein at least two films of different compositions are rolled up to form a tubular or rod-like member.

20. A process for the preparation of an implant as claimed in claim 1 which process comprises extruding a mixture of said carrier material, physiologically active substance and additive

material and forming the extrudate into tubular or rod-like members of desired dimensions.

21. A process as claimed in claim 15, 16 or 17 wherein said tubular or rod-like member is provided with an outer casing.

22. A composition which comprises a poly-lactide carrier material, a physiologically active substance and an additive material selected from pore-forming agents, low molecular weight polymer and physiologically acceptable solvents and plasticizers in an amount up to 10% by weight based on the weight of carrier material.

23. Use of a biodegradable implant containing a physiologically active substance as claimed in any one of claims 1 to 3 and 8 to 11 for treatment of the human or non-human animal body.

FETHERSTONHAUGH & CO.
OTTAWA, CANADA

PATENT AGENTS

B

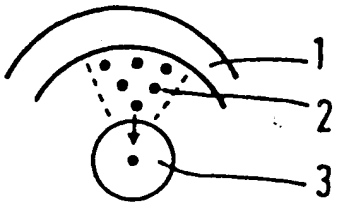


FIG.1.

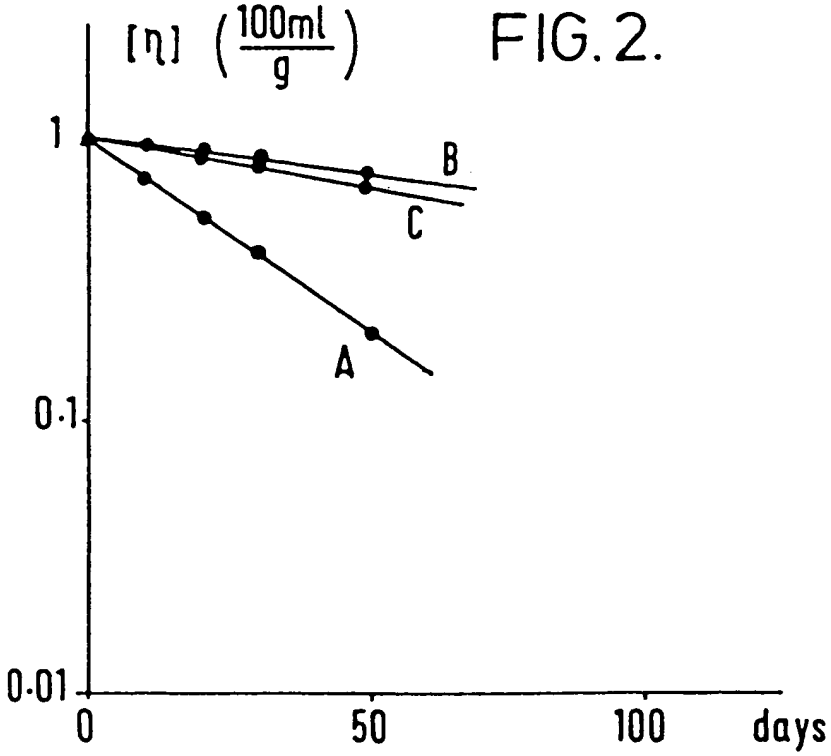


FIG.2.

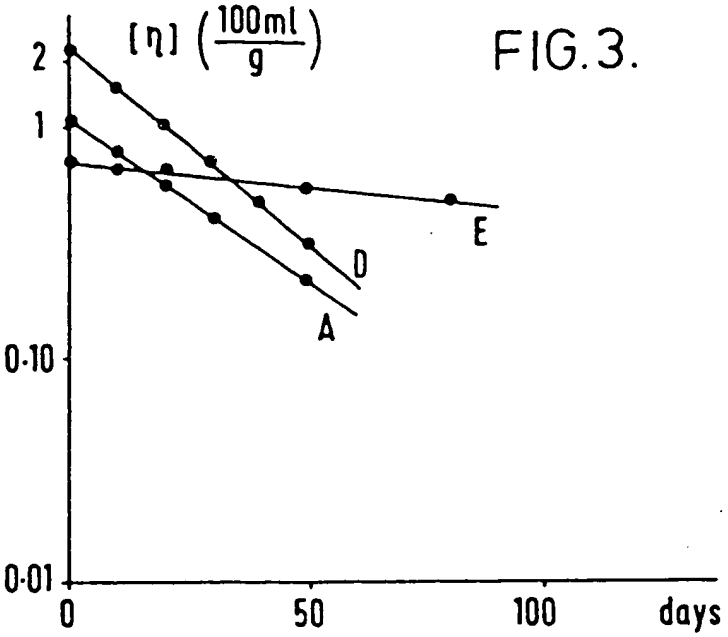

[η] (100ml/g)
2
1
0·10
0·01
0
50
100
days
E
D
A

FIG.3.

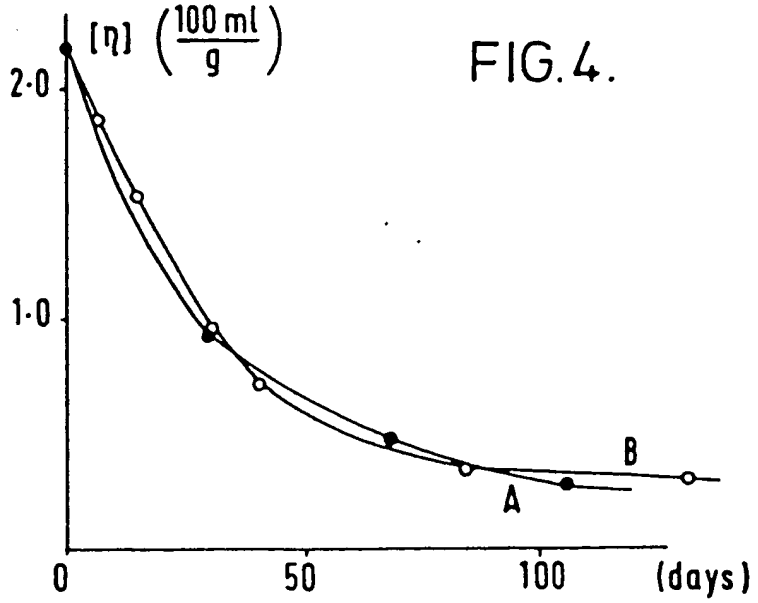

[η] (100 ml/g)
2·0
1·0
0
50
100
(days)
B
A

FIG.4.

FIG.5.

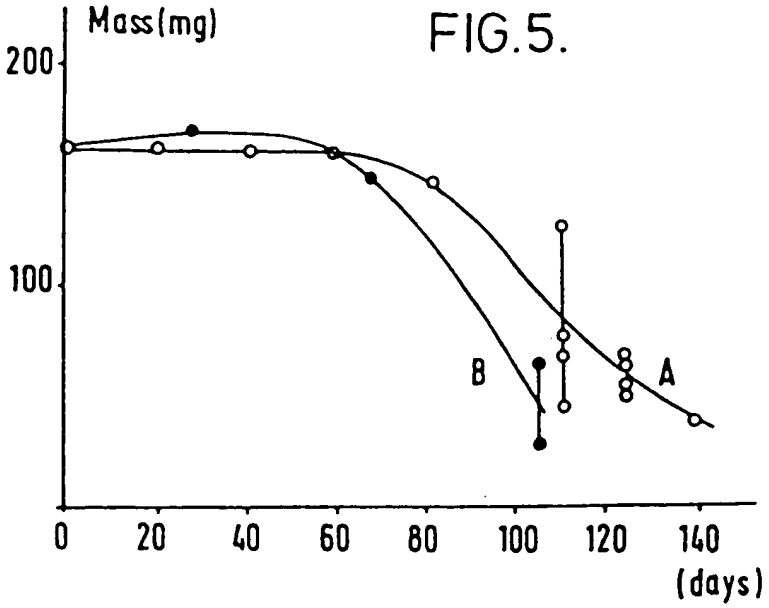
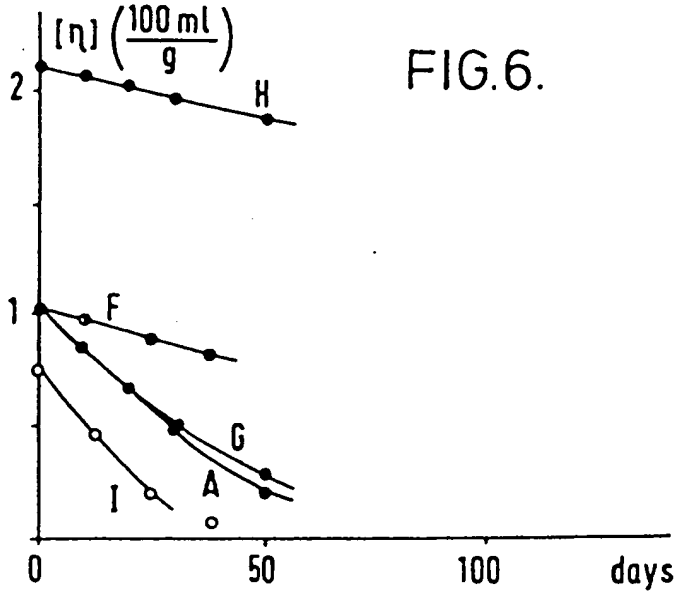

Mass(mg)
200
100
B
A
0
20
40
60
80
100
120
140
(days)

FIG.6.


[η] (100 ml / g)
2
H
1
F
G
A
I
0
50
100
days

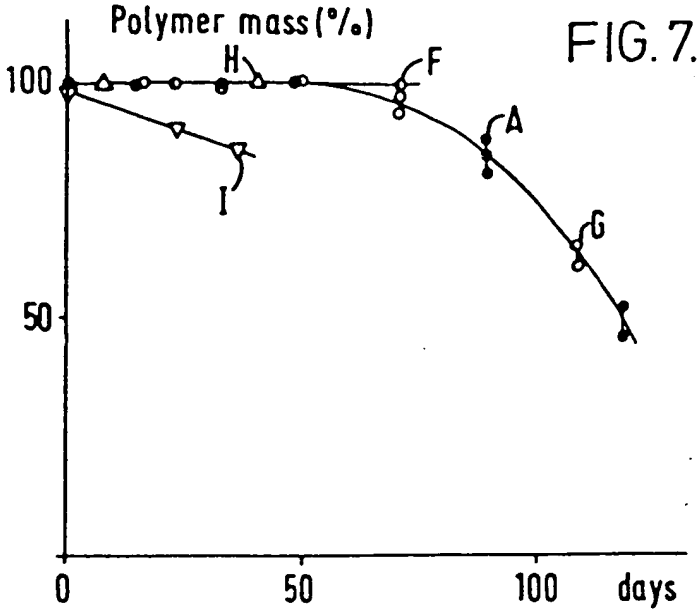

Polymer mass (%)
100
50
H
F
A
G
I
0
50
100
days

FIG. 7.

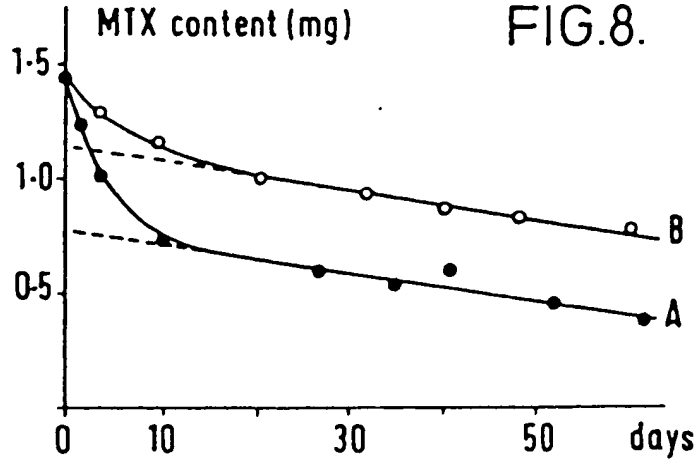

MTX content (mg)
1·5
1·0
0·5
B
A
0
10
30
50
days

FIG. 8.

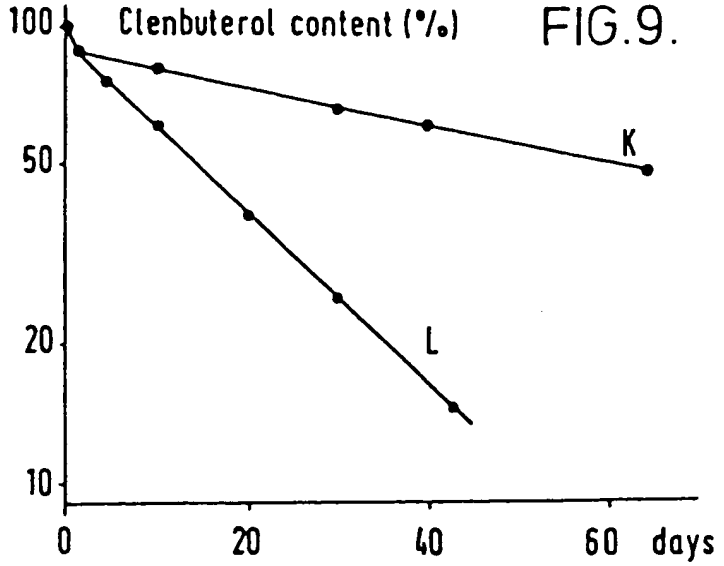

Clenbuterol content (%)
100
50
20
10
0
20
40
60 days
K
L

FIG.9.

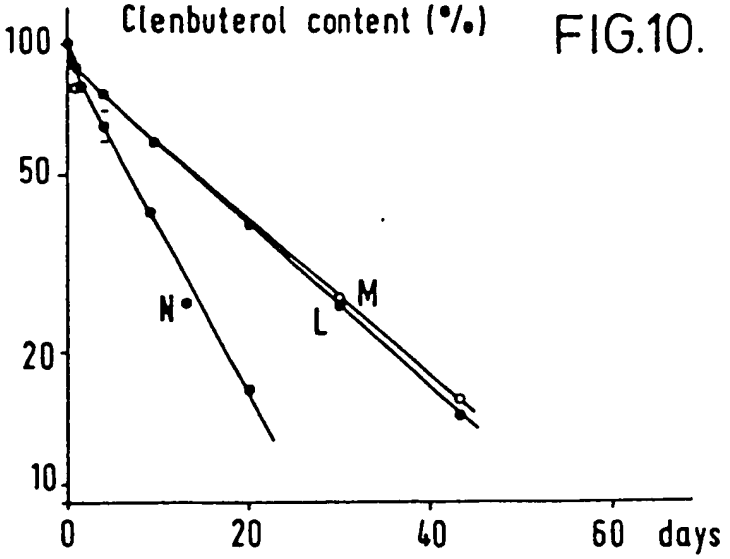

Clenbuterol content (%)
100
50
20
10
0
20
40
60 days
N
L
M

FIG.10.

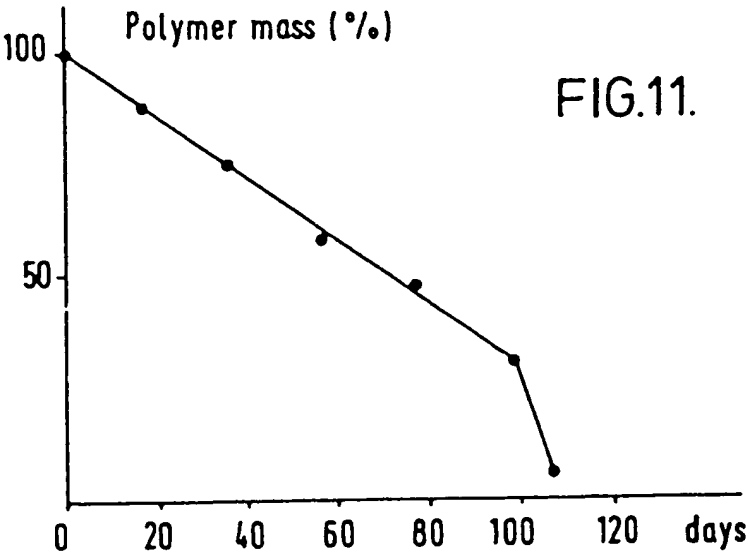

Polymer mass (%)
100
50
0
20
40
60
80
100
120
days

FIG.11.

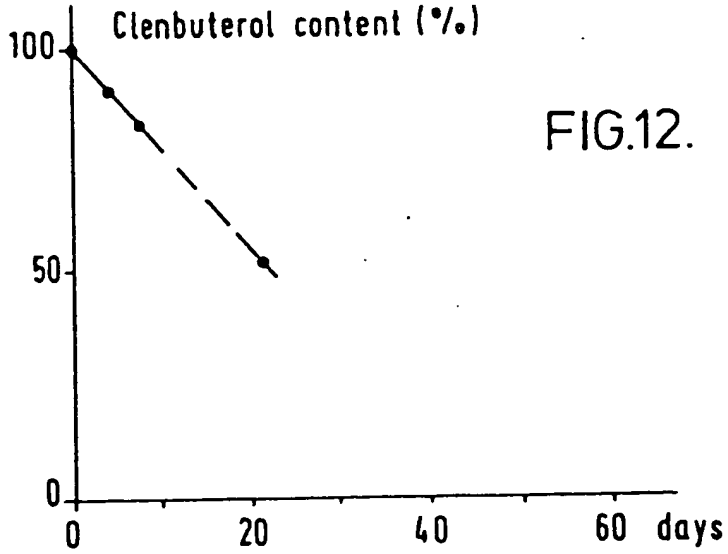

Clenbuterol content (%)
100
50
0
0
20
40
60
days

FIG.12.